OVERVIEW

Diabetes mellitus is the leading cause of kidney failure, blindness in adults, and amputations. It is a major risk factor for heart disease, stroke, and birth defects. Diabetes shortens average life expectancy by 10 to 15 years, and costs the nation in excess of $100 billion annually in health related expenditures. The cost in terms of human misery for patients and their families cannot be measured.

Recognizing the enormity of the problems posed by diabetes, the U.S. Congress, in 1997, mandated formation of the Diabetes Research Working Group (DRWG) and directed it to develop a comprehensive Research Plan for all diabetes research funded by the National Institutes of Health. Following a year-long planning process, the Diabetes Research Working Group concluded that the rapid advances in diabetes-related research made possible by a wide array of new technologies have set the stage for a major national effort to conquer diabetes and that to capitalize upon these unprecedented opportunities, a significant increase in funding of diabetes research above the current levels is needed now. The Diabetes Research Working Group, which is made up of a group of nationally-known experts in the field presents its conclusions in "Conquering Diabetes: A Strategic Plan for the 21st Century."

The plan has three major components and includes recommendations for the types of efforts that will be needed if we are to succeed in the fight against diabetes. The components of the plan are:

- Extraordinary Opportunities;
- Special Needs for Special Problems; and
- Resource and Infrastructural Needs

EXTRAORDINARY OPPORTUNITIES

The Diabetes Research Working Group has identified five areas of diabetes research in which the current rapid expansion of knowledge and development of new technologies make it likely that intensified research efforts at this time would lead to significant advances in the near future. These areas of extraordinary opportunity are:

- Genetics of diabetes and its complications;
- Autoimmunity and the beta cell;
- Cell signaling and cell regulation;
- Obesity research; and
- Clinical research and trials of critical importance.

SPECIAL NEEDS FOR SPECIAL PROBLEMS

Diabetes is a complex cluster of disorders that cause and are caused by special problems that require special research focus. These are:

- The micro- and macrovascular complications of diabetes;
- Methods to optimizing glucose control;
- Studies of the environmental factors that cause diabetes;
- Research on diabetes in women, children, and the elderly;
- Research on diabetes in minority populations;
- Genetic engineering; and
- Behavioral and health services research.

RESOURCE AND INFRASTRUCTURAL NEEDS

The Diabetes Research Working Group has attempted to specifically address limitations in current NIH programs and mechanisms and proposed new approaches and significant changes in existing programs that would greatly facilitate the research process. These include:

- Strengthening research training and human resources development;
- Enhancement of the Diabetes Research Centers program;
- Developing and harnessing new technologies;
- Animal models for the study of diabetes;
- Enhancing mechanisms for obtaining human materials for diabetes research;
- NIH-pharmaceutical and biotechnology interactions; and
- Optimizing diabetes research activities through strategic planning.

EXTRAORDINARY OPPORTUNITY: GENETICS OF DIABETES AND ITS COMPLICATIONS

The explosive advances in genetic technology are revolutionizing medical research, including diabetes research. For over 100 years, heredity has been known to play an important role in diabetes. Only recently, however, have researchers been able to begin to identify particular culprit genes and use sophisticated technologies to discover the roles they play in causing diabetes and its numerous devastating complications. As the incredibly rapid pace of discovery in the field of genetics continues to quicken, an enormous opportunity exists to solve the puzzle of the genetics of diabetes. As each piece of the puzzle is filled in, it will be possible to design better ways to treat, prevent, and even cure diabetes.

Type 1 diabetes, for example, is an autoimmune disease in which the immune system mistakenly identifies the body's insulin-producing beta cells as foreign and destroys them. Researchers now know that some of the genes responsible for the immune response are located on chromosome 6 and that molecules produced by these genes can be detected in patients. In fact, 85 to 90 percent of people with Type 1 diabetes have these molecules, and people who do not have diabetes--but have the molecules--are more likely than people without them to develop the disease. As more of the genes related to Type 1 diabetes are discovered and studied, it will be possible to screen people accurately for the disease and to identify those who are candidates for preventive therapy, including gene therapy.

Genetic factors may be even more critical in Type 2 diabetes than in Type 1. Type 2 diabetes comes in many forms, and multiple genes appear to be involved in each. Some genes for several rare forms of the disease have been identified. However, the genes involved in the most common varieties of Type 2 diabetes remain unknown. Ongoing genetic research and expanded population studies--including African and Native American populations who are at especially high risk for Type 2 diabetes--should be able, in the near future, to identify one or more of the common genes responsible, and to determine their relationship to Type 2 diabetes and to associated problems, such as obesity, hypertension, and atherosclerosis.

The devastating, long-term complications of diabetes, especially diabetic kidney disease and vascular disease, also appear to be genetically determined, and may also soon yield to the advances being made in genetic research. In fact, the Diabetes Research Working Group believes that "genetic studies offer the single best opportunity for identification of the unknown causes of complex diseases, such as diabetes."

To take advantage of the extraordinary research opportunities presented by this unprecedented explosion of information and new technologies in genetic research the Diabetes Research Working Group recommends:

- Establish a National Consortium for the Study of the Genetics of Diabetes, which brings together researchers throughout the U.S. with differing expertise and adequate resources to solve this problem; and

- Enhance research efforts to discover how diabetes genes create susceptibility to the disease and its complications.

EXTRAORDINARY OPPORTUNITY: AUTOIMMUNITY AND THE BETA CELL

In Type 1 diabetes, for as yet unknown reasons, the body attacks itself. The immune system, which is designed to combat foreign invaders, such as bacteria, mistakenly identifies the insulin-producing beta cells of the pancreas as alien and destroys them. This so-called autoimmune response is at the heart of Type 1 diabetes. Research is making great strides in unraveling the mystery of why and how this happens, but much remains to be learned if we are to understand and control the autoimmune response. We must find ways to prevent the self-destruction of the beta cells and restore normal islet cell function by replacing the cells or by stimulating the growth of new cells.

Basic research in immunology, cell biology, and autoimmune diseases is beginning to pay off in terms of strategies toward preventing, and eventually curing, Type 1 diabetes. Researchers have identified several targets (antigens), including insulin that the immune system attacks. This work is in the early stages, but the NIH is already testing whether an "antigen-based therapy" with insulin can prevent or slow the progression of Type 1 diabetes, by allowing susceptible individuals to develop immune "tolerance." Research is also progressing on use of immune-system proteins, such as cytokines and monoclonal antibodies that suppress the immune response. Success in these efforts might help prevent diabetes as well as help block rejection of transplanted tissue, including islet tissue that produces insulin.

Islet transplantation is expected to be an important therapy to replace the damaged beta cells in Type 1 diabetes. Thousands of patients have had successful pancreas transplants, but this is not expected to be a treatment of choice, because the surgery is difficult and risky, patients require constant immunosuppression therapy, and the number of donor organs is limited. The focus, instead, is to give only the missing beta cells by islet transplantation. Although more than 100 patients have had islet transplants, so far there has been limited success. Researchers are now focusing on how to make the procedure more successful. Human, animal, and genetically engineered islets are being studied, as are methods of encapsulating the islets, to protect them from the immune system.

An even simpler approach to restoring insulin production, if it can be achieved, would be to stimulate new islet growth or insulin secretion. Success in these lines of research would solve the problem of shortages of donor tissue and the problem of rejection, because the patients' own cells would be used.

Based on recent progress in understanding and controlling the autoimmune process and on the potential for developing effective islet transplantation or islet growth therapy, the Diabetes Research Working Group recommends:

- Intensify efforts to understand the immunological basis of Type 1 diabetes, including conduct of clinical trials on immune prevention;

- Create centers and intensify research on islet cell transplantation; and

- Expand basic research to develop methods to stimulate beta cell growth or regeneration.

EXTRAORDINARY OPPORTUNITY: CELL SIGNALING AND CELL REGULATION

Type 2 diabetes represents a failure of cells to communicate. In Type 1 diabetes, the body attacks itself. In Type 2, the body does not listen to itself. Defects in cell-to-cell communication lead to a decrease in the ability of liver, muscle, and fat tissue to respond to insulin--a phenomenon known as insulin resistance. In addition, the insulin-producing beta cells fail to respond normally to the high glucose levels created by insulin resistance. Signaling defects also play a basic role in obesity and other complications caused by diabetes.

During the past decade significant progress has been made in understanding cell-to-cell and within-cell signaling and what goes awry in diabetes. Powerful new technology now available in biochemistry, physiology, cell and molecular biology, and structural biology is beginning to shed light on insulin signaling, beta cell functioning, hormonal control of body weight, and even on the autoimmune response in Type 1 diabetes. These discoveries are helping researchers understand cell communication in ways that should lead rapidly to the development of new drugs to treat diabetes. Together with ongoing developments in genetics, discoveries in cell signaling and regulation offer the greatest prospect for preventing and treating diabetes and its consequences.

For example, discovering the defects in insulin action, which are among the earliest signs of Type 2 diabetes, will create unprecedented opportunities to combat insulin resistance and possibly to design drugs that mimic insulin action. Such drugs would be useful in treating all types of diabetes.

Cell signaling research also holds great potential for determining the abnormalities that lead to altered and insufficient insulin secretion and to hyperglycemia in diabetes. Continued advances in this area will be essential for developing a supply of beta cells for transplant therapy for Type 1 diabetes and for correcting the defects in beta cell functioning in Type 2 diabetes.

The slow and progressive development of diabetes suggests that there are signaling abnormalities in other tissues, such as muscle, liver, and fat. Defining and detecting these abnormalities could lead to simple and accurate markers of the progression of the disease. With such information, physicians would be able to monitor the stages of the disease, the clinical status of patients, and to tailor therapy more effectively. Precise metabolic staging may also be used to detect persons at high risk for Type 2 diabetes and its complications, and will be critical in developing and testing new therapies for diabetes.

The microvascular complications of diabetes, such as diseases of the eye, kidney, and nervous system, also involve defects in cell signaling that researchers are beginning to understand and to develop drugs to correct. Cell signaling research is the key to new drug development. The Diabetes Research Working Group recommends:

- Increased research on cell signaling as it relates to diabetes and its complications;
- Remove current limits on research grants in order to maximize the opportunity for effective research teams to be formed;
- Establish research centers that focus on cell signaling at the molecular and genetic level in persons with diabetes;

- Expand research to identify the underlying genetic and biochemical bases of insulin resistance and develop interventions to prevent or reverse it;

- Increase research on signaling pathways involved in regulation of beta cell functioning;

- Develop accurate metabolic staging of Type 2 diabetes for detecting the disease and its complications in persons at high risk; and

- Expand support of interdisciplinary research on the complications of diabetes.

EXTRAORDINARY OPPORTUNITY: OBESITY RESEARCH

The epidemic of obesity in this country is a significant health problem. One of every two Americans is overweight. Obesity, which now affects more than one of every three Americans, is a major risk factor for Type 2 diabetes and insulin resistance. It is also related to hypertension, atherosclerosis, and coronary heart disease. Finding effective ways to treat and prevent obesity would solve one of the nation's major health problems and go a long way toward preventing or alleviating Type 2 diabetes.

In people of normal weight, eating and energy expenditure is delicately balanced by body signals that control appetite and energy expenditure. In many obese people, these signals do not function properly. For example, recent research has shown that fat actively secretes leptin, a hormone that appears to play an active role in appetite, energy storage, and energy expenditure. Leptin and several other chemical and hormonal messengers act on the brain to either stimulate or suppress appetite and energy output. They help determine how hungry or full a person feels and how likely a person is to eat in response to that feeling. Recent research has also uncovered new mechanisms used by the body to regulate energy expenditure, the other side of the equation. This explosive increase in understanding the molecular mechanisms involved in obesity suggests that it may soon be possible to design drugs that control appetite and help prevent obesity and Type 2 diabetes.

Molecular research has great potential, but controlling chemical messages is not the only way to treat obesity. Like diabetes, obesity is the result of an interplay between genes and the environment. Researchers have already discovered several genetic defects that can lead to obesity and have shown clearly that environmental factors play a major role in obesity and diabetes. Nearly half the Pima Indians of Arizona, for example, have diabetes. By contrast, their counterparts in rural Mexico have almost no diabetes. They share genes, but they have different environments and lifestyles. The Pimas in Mexico eat a low-fat diet, have a strenuous life style with a great deal of physical activity, and are thin. Those in Arizona have a more "westernized" lifestyle, live a more sedentary life, eat a high-calorie diet, and are obese.

Although diet and lifestyle are well known to be risk factors for obesity and diabetes, little is really known about how to control these factors effectively. Diets and exercise programs help, but success rates are low. To prevent obesity and treat those already affected, truly multidisciplinary efforts involving research in such areas as genetics, neuroscience, endocrinology, and behavioral medicine, are needed. The Diabetes Research Working Group recommends:

- Increase the size, scope, and number of NIH-sponsored Obesity Research Centers;
- Increase fundamental research to capitalize on recent advances in hormonal control of appetite, energy regulation, and metabolism;
- Develop stronger industry-NIH relationships to support obesity research; and
- Enhance behavioral research on obesity.

EXTRAORDINARY OPPORTUNITY: CLINICAL RESEARCH AND CLINICAL TRIALS OF CRITICAL IMPORTANCE

Much of the recent rapid progress in diabetes research has resulted from studies done in test tubes or with animals. The next step in translating these findings into useful therapies for the prevention and treatment of the disease is clinical research--studies in patients with diabetes. Clinical studies are essential for validating the findings made through basic research and for testing potential new therapies through clinical trials. Clinical research can yield key insights into the genetic, immunological, hormonal, metabolic, and environmental factors involved in diabetes. Clinical research and clinical trials, however, are time consuming and expensive, especially with diseases as complex as diabetes and its complications. The Diabetes Control and Complications Trial (DCCT), for example, showed clearly that precise control of blood glucose levels reduces the long-term complications of the disease. The DCCT was a 10-year investigation into the relationship between intensive insulin therapy and the microvascular complications of diabetes. The study involved 27 research groups at top medical centers in the United States and Canada. More than 1,400 patients took part in the DCCT.

Despite the high costs of such clinical studies, they are essential to developing the knowledge needed to effectively treat and prevent diabetes and its complications. Unfortunately, recent years have seen a significant decrease in clinical research on diabetes. Fewer clinical investigators, limits on funding for clinical research, and the complexity and long-term nature of the disease are among the reasons for the decrease in clinical studies. Furthermore, the infrastructure necessary for organizing, coordinating, and conducting effective and efficient clinical trials is lacking. The Diabetes Research Working Group is convinced that these problems must be overcome and that any comprehensive plan to tackle a major public health problem, such as diabetes, requires a major effort in both basic and clinical research. Clinical trials are particularly important for documenting the safety and efficacy of various therapies and for developing a knowledge base that will lead to better treatment of the disease and improved care of people with the disease. The Diabetes Research Working Group recommends:

- Creation of Diabetes TrialNet, a network of clinical research groups that would provide the stable, high-quality infrastructure needed to conduct effective and efficient clinical trials;

- Enhanced support for meritorious clinical trials of emerging new therapies for diabetes;

- Support clinical trials on the prevention and treatment of cardiovascular, kidney, eye, and nerve disease, which are all accelerated in diabetes.

- Foster partnerships among the NIH, academia, and industry for collaboration on clinical trials; and

- Support clinical research training in diabetes.

SPECIAL NEEDS FOR SPECIAL PROBLEMS

Diabetes is a complex cluster of disorders that cause and are caused by special problems that require special research focus. These are:

- The micro- and macrovascular complications of diabetes;
- Methods to optimize glucose control;
- Studies of the environmental factors that cause diabetes;
- Research on diabetes in women, children, and the elderly;
- Research on diabetes in minority populations;
- Genetic engineering; and
- Behavioral and health services research.

SPECIAL NEEDS FOR SPECIAL PROBLEMS: MICROVASCULAR COMPLICATIONS OF DIABETES--A MAJOR CAUSE OF DISABILITY

Both Type 1 and Type 2 diabetes can cause widespread damage to small blood vessels throughout the body and lead to what are known as microvascular complications, such as kidney, eye, and nerve diseases. Because these conditions can be so serious, debilitating, and incapacitating, they deserve special research attention.

Diabetic kidney disease, or nephropathy, for example, accounts for more than 40 percent of all new cases of kidney disease and is the leading cause of the need for dialysis. It results from damage to the small blood vessels that supply oxygen and nutrients to the kidneys and filter out toxic wastes. Inability to remove certain substances leads to an imbalance that causes the kidneys to malfunction. Current therapy for diabetic nephropathy involves improved glucose control and the use of drugs that change blood flow patterns in the kidneys. This combination of therapies can help prevent or delay onset of the disease, but many patients progress to kidney failure.

On the other hand, patients who have had successful pancreas transplants sometimes show signs of healing, which suggests that the damage caused by diabetic nephropathy can be partially reversed. Understanding the mechanisms by which this healing takes place could lead to new ways to treat and prevent the disease. Research on other aspects of the disease and on the genes involved could also lead to new forms of drug therapy. In pursuit of these goals, the Diabetes Research Working Group recommends:

- Intensify studies of the basic mechanisms involved in diabetic nephropathy and develop strategies to prevent or reverse it; and

- Establish multidisciplinary centers to expand basic and clinical research on diabetic kidney disease.

Diabetic eye disease, or retinopathy, is the leading cause of new blindness in people 20 to 74 years of age. It is caused by damage to the small blood vessels and nerves in the eye. Various biological mechanisms, including hormones, growth factors, and other molecules, as well as reduced blood flow to the retina, appear to be involved in retinopathy. Because the eye is easily accessible for evaluation and treatment, it may be possible to develop tissue-specific treatments, including gene therapy, to reverse the biological or functional changes caused by diabetic retinopathy. Advances in understanding the neurophysiology of the retina and the visual pathways in the brain may also lead to the development of prosthetics and transplantation technology for retinopathy. In order to achieve the goal of curing or preventing diabetic eye disease, the Diabetes Research Working Group recommends:

- Increase basic and clinical research on the roles of hormones, growth factors, and other molecules in the development of diabetic retinopathy;
- Increase research on the potential for tissue-specific gene therapy, drug therapy, and nerve regeneration to treat retinopathy; and
- Increase research to improve prosthetics and transplantation technology for diabetic retinopathy.

Diabetic nerve disease, or neuropathy, is an urgent, special need in diabetes research. It is the

least understood of the complications of diabetes, but it causes significant problems for up to 60 percent of diabetes patients at some time in their lives. It causes pain and loss of sensation in the peripheral nervous system and can interfere with autonomic nervous system functions, such as digestion and sexual response. The mechanisms involved are probably similar to those involved in other microvascular complications, but this has been difficult to prove because the nervous system is very difficult to study. What is known is that the peripheral nervous system is capable of at least some degree of regeneration following disease or injury. Researchers have also discovered a number of nerve growth factors that promote nerve health and may be useful in treating both neuropathy and diabetic eye disease. Although much work needs to be done, these and other recent developments make nerve regeneration a realizable goal. Investment in such research would be would be of great benefit to patients with diabetic neuropathy and possibly to those with late-stage eye disease. The Diabetes Research Working Group recommends:

- Increase research on the mechanisms involved in nerve damage;
- Increase research on nerve regeneration; and
- Establish multidisciplinary centers to study metabolic nerve disorders, including diabetic neuropathy.

SPECIAL NEEDS FOR SPECIAL PROBLEMS: MACROVASCULAR COMPLICATIONS--THE MAJOR KILLER OF PEOPLE WITH DIABETES

Diabetes causes damage to the large blood vessels--resulting in what is known as macrovascular complications. These include heart attack, stroke, and atherosclerosis. These complications are the major killers of people with diabetes and are responsible for shortening the average life span by as much as 15 years. Much remains to be learned about the causes of these complications, but knowledge generated during the past decade is providing compelling opportunities to develop effective interventions against them.

Little is known, for example, about how diabetes causes atherosclerosis and cardiovascular disease. However, advances in the exciting area of genetic research may soon make it possible to develop animal models with both diabetes and atherosclerosis, or other cardiovascular abnormalities. Such animal models, which closely mimic human diabetes, could help answer many questions about the disease.

Another area that deserves special attention is angiogenesis, the growth of new blood vessels. Clinical studies have shown that angiogenic growth factors can be used to beneficially stimulate blood vessel growth and increase blood flow in the heart and other parts of the body. However, blood vessel growth in some parts of the body, such as the eyes, can have a negative effect. Learning how to control angiogenesis locally, and how to enhance or retard new blood vessel growth in different parts of the body could lead to important new therapies.

Other areas that need special attention include efforts to better predict which diabetic patients will develop macrovascular complications; efforts to understand why diabetic patients with coronary artery disease are twice as likely to have heart attacks as are those without diabetes; and efforts to understand the link between insulin resistance and atherosclerosis and cardiovascular disease. Understanding these and other mechanisms that contribute to the macrovascular complications of diabetes is critical in efforts to prevent and treat them. The Diabetes Research Working Group recommends:

- Increase research on how diabetes and insulin resistance lead to accelerated atherosclerosis;
- Increase research on angiogenesis and its use in treating and preventing macrovascular complications;
- Increase basic and clinical research on cardiovascular disease and identify factors that lead to excessively high mortality rates in patients with diabetes and cardiovascular disease;
- Support research to develop appropriate animal models with diabetes and atherosclerosis;
- Support research on ways to better predict which diabetic patients will develop macrovascular complications; and
- Establish Multidisciplinary Centers for Diabetes and Vascular Disease.

SPECIAL NEEDS FOR SPECIAL PROBLEMS: OPTIMIZING GLUCOSE CONTROL

Tight control of blood glucose levels can significantly reduce complications of diabetes in both Type 1 and Type 2 diabetes. However, keeping glucose levels as close to normal as possible is extremely difficult for most patients, and many continue to develop the life-threatening micro- and macrovascular complications of the disease. Tight control of glucose levels also runs the risk of hypoglycemia, or low blood sugar, when patients take too much insulin. Severe hypoglycemia can seriously impair a person's ability to function and even cause them to lose consciousness. Because current methods of controlling glucose levels--measuring glucose by painful finger pricks and then taking insulin--are difficult and often do not achieve good glucose control, research on better ways to control glucose levels is an area of extremely high priority. Such research should focus on more accurate and less invasive ways to monitor glucose levels, on ways to help patients be more aware of changes in their blood sugar, and on development of more effective methods for achieving glucose control.

One approach to more precise insulin use involves mechanical insulin pumps that patients control. Many patients have used such pumps for many years and studies have shown that the pumps have significant advantages over multiple daily injections of insulin. More reliable insulin pumps are being developed. Ultimately the goal is to develop an "artificial pancreas," in which an implantable insulin pump is linked to a glucose sensor to deliver insulin just like a normal pancreas, without patient involvement. The NIH has supported research in this area for a number of years, but a reliable glucose sensor that can be linked with the insulin delivery system has yet to be developed.

Other methods of insulin delivery, such as islet transplants, are also being developed. Researchers are trying to develop molecules that mimic insulin action and are small enough to be taken orally. Research is also needed on the design of molecules that overcome the insulin resistance seen in Type 2 diabetes and on drugs that stimulate the production of insulin. Progress is being made in these areas, but increased efforts are needed. The Diabetes Research Working Group recommends:

- Increase basic and clinical research on novel approaches to control of hyperglycemia;
- Develop a multidisciplinary research program to focus on hypoglycemia; and
- Intensify research on mechanical devices for insulin replacement.

SPECIAL NEEDS FOR SPECIAL PROBLEMS: DIABETES AND THE ENVIRONMENT

Type 1 diabetes is well known to have a genetic basis, but genes alone do not explain who gets the disease. Identical twins, for example, share the same genes but do not get Type 1 diabetes with the same frequency. In fact, in fewer than 50 percent of the cases do both twins get the disease. This suggests that environmental factors play an important role in diabetes in genetically susceptible persons. However, the environmental factors that trigger Type 1 diabetes are not known. They may be infectious agents, dietary factors, or other environmental substances. Identifying the environmental factors in Type 1 diabetes should be a primary research goal. The Diabetes Research Working Group recommends:

- Hold a series of conferences or workshops to explore new ways to search for environmental triggers of diabetes;

- Conduct an epidemiologic study of substances suspected of triggering the autoimmune process; and

- Explore with the Centers for Disease Control and Prevention the possibility of establishing a national registry for Type 1 diabetes as a way of enhancing epidemiological research.

Type 2 diabetes also has a strong environmental component, and some of the factors involved, such as decreased levels of physical activity, decreased consumption of complex carbohydrates, increased intake of calories and fat, and accompanying obesity are known. In some populations with a strong predisposition for Type 2 diabetes, the disease is rare unless these environmental factors are also present. This is most clearly seen in populations, such as the Pima Indians of Arizona, who have undergone a rapid "westernization" in their life styles. There is also evidence that poor maternal nutrition can affect the fetus and lead to Type 2 diabetes when the children of these women become adults. Although life style factors are known to be involved in Type 2 diabetes, it is not possible to say which are more responsible for susceptibility to the disease because it is very difficult to measure accurately energy intake and expenditure under uncontrolled circumstances. To clarify the role of environmental factors in Type 2 diabetes, the Diabetes Research Working Group recommends:

- Develop new technologies to measure accurately energy intake and expenditure; and

- Initiate epidemiologic studies to help identify additional environmental risk factors, such as stress levels and infectious agents.

SPECIAL NEEDS FOR SPECIAL PROBLEMS: DIABETES IN WOMEN, CHILDREN, AND THE ELDERLY

Diabetes presents special challenges to women, children and the elderly. Women, for example, are at increased risk for diabetes during pregnancy. For women who are already pregnant, pregnancy poses increased health risks for them as well as for their unborn children. Much of this increased risk could be avoided if women with diabetes took part in family planning and preconception diabetes care, but most women with diabetes do not participate in such programs. Behavioral research is critically needed to understand and address this problem.

Greater research is also needed on gestational diabetes mellitus (GDM), a form of diabetes that occurs during pregnancy. More than 100,000 women get GDM every year, and half of them go on to develop Type 2 diabetes later in life. Women with diabetes are also at greater risk for heart disease than are women without diabetes because they do not have the normal protective effect of estrogen. More research is needed to understand this phenomenon, as well as the link between insulin resistance and polycystic ovarian disease.

Perhaps the cruelest facet of diabetes is seen in children. Children of diabetic pregnancies are at increased risk for diabetes, obesity, and cardiovascular disease later in life. Type 1 diabetes, which is often diagnosed in infancy, can be especially cruel. Children with the disease face a life time of daily insulin injections. In addition, complications of diabetes can be especially severe because they tend to worsen as the disease progresses.

Diabetes also poses extremely serious problems for the elderly. People over the age of 55 with diabetes are more likely than those without the disease to have higher rates of cardiovascular disease, stroke, kidney disease, nerve disease, cataracts, and glaucoma. They also have higher rates of diabetes-associated risk factors, such as obesity and hypertension. Research is needed on the effects of age-related changes on Type 2 diabetes in the elderly and on the effects these changes have on prevention and treatment strategies.

In order to address the special needs of women, children, and the elderly more fully, the Diabetes Research Working Group recommends:

- Increase basic and clinical research on how the intrauterine environment, including the diabetic environment, affects the long-term health of children;
- Support research on the impact of diabetes on women's reproductive health, cardiovascular disease, and the risk of diabetes following GDM;
- Increase studies of psychosocial issues that face women, children, and the elderly, including eating disorders, the impact of school settings, and the management of diabetes in assisted-living conditions;
- Increase studies of ways to control glucose levels more effectively in children and help reduce complications from the disease; and
- Increase studies of how age-related changes affect diabetes and efforts to treat and prevent it.

SPECIAL NEEDS FOR SPECIAL PROBLEMS: MINORITY POPULATIONS

More than half the Pima Indians of Arizona have Type 2 diabetes. African Americans, Hispanic Americans, and Native Americans have rates of diabetes that are nearly double that of those of Caucasian Americans. Not only are these minority populations at increased risk for diabetes, but also there has been an alarming increase in the number of minority children with diabetes. The reasons for such high rates of the disease among these populations are not entirely clear, but the results can be devastating, especially because the complications of diabetes are more common in minority populations. The prevalence of diabetic eye disease (retinopathy) is 50 percent higher among African Americans, 80 percent higher among Mexican Americans, and up to 100 percent higher among some Native Americans with diabetes than among non-Hispanic Caucasian Americans. Rates of cardiovascular disease, kidney disease, and lower limb amputations are also elevated in minority populations. Because it appears that the majority of cases of diabetes are due to gene-environment interactions, there is a pressing need to identify and better understand these factors, including life style factors, that may be related to development of diabetes and may affect its treatment in minority populations. The Diabetes Research Working Group recommends:

- Increase genetic studies of diabetes in minority populations;
- Support research to identify other physiologic and environmental factors related to Type 2 diabetes and its complications in minority populations, including children and adolescents;
- Develop culturally-sensitive education, prevention, and treatment programs for use in rural and urban health centers; and
- Design and conduct studies in partnership with minority communities to better understand the cultural, familial, and other factors that influence health-related behaviors in minority populations at risk for Type 2 diabetes.

SPECIAL NEEDS FOR SPECIAL PROBLEMS: GENETIC ENGINEERING

The rapid advances being made in genetic research open the way to the possibility of screening people for diabetes and to the design of genetic therapies to prevent and treat the disease and its complications. The Diabetes Research Working Group believes there are several other areas of genetic research that also hold great promise. It should be possible in the near future, for example, to use bioengineering techniques to create cell lines that simulate the function of normal beta cells. Eventually, such cell lines could be grown in very large numbers to solve the problem of cell supply for transplant therapy. Important advances are also being made in efforts to genetically engineer cell lines that would be protected against attack by the immune system in Type 1 diabetes.

In addition to developing ways to replace beta cells, advances are being made in efforts to use genetic engineering techniques to design therapies for specific complications of diabetes. In fact, ongoing progress in this area suggests that gene therapy for Type 2 diabetes may be more feasible than for other complex disorders. The Diabetes Research Working Group recommends:

- Increase support of research on possible ways to use genetic engineering as a strategy for beta cell replacement and immunoprotection of transplanted cells;

- Support research on the potential of gene therapy for Type 2 diabetes; and

- Support research on unique applications of gene therapy to treat micro- and macrovascular complications of diabetes.

SPECIAL NEEDS FOR SPECIAL PROBLEMS: BEHAVIORAL AND HEALTH SERVICES RESEARCH

Behavioral and health services research is critically needed to better understand the impact of diabetes on individuals and their families and to identify effective ways of ensuring that the most up-to-date, effective therapies are available, tailored to, and utilized by all populations. Tight control of glucose levels is important for delaying or decreasing the severity of the complications of diabetes, but many patients find it difficult to follow the strict regimen necessary to achieve such control. What is needed is a better understanding of the behavioral and psychosocial factors that foster or impede adherence to the regimen, as well as better and easier methods of glucose control.

In many cases, success depends on changing the behaviors of patients, physicians, and persons at risk for diabetes. Diet, exercise, smoking, and other lifestyle factors are also implicated in diabetes and its complications. Although some behavioral programs are effective in changing such behaviors, most have only minimal or short-term effects. Behavioral interventions that produce sustained changes in lifestyle behaviors are sorely needed in the battle against diabetes. More effective behavioral treatments are also needed for depression, stress, eating, and other disorders that may increase the risk of diabetic complications. In addition, the psychosocial difficulties created by diabetes and its complications need to be addressed more effectively.

Health services research is another important component of the overall effort to combat diabetes and its complications. Health services research focuses on the effectiveness and quality of health care for diabetes and on efforts to assure that access to care is available.

The Diabetes Research Working Group recommends:

- Support clinical behavioral research to develop interventions to improve patient adherence to diabetes treatment and promote sustained improvements in lifestyle behaviors;

- Support research on ways to measure more accurately psychosocial and behavioral factors related to diabetes;

- Integrate behavioral and pharmacological efforts to reduce risk factors for diabetes and its complications;

- Develop interdisciplinary research and training programs that combine expertise in the behavioral sciences with expertise in diabetes, nutrition, and exercise physiology; and

- Study the effectiveness of different clinical practices, interventions, and technologies, and identify deficiencies in access to health care for diabetic patients.

RESOURCE AND INFRASTRUCTURAL NEEDS

An effective program of diabetes research can exist only if there is a supportive infrastructure. The Diabetes Research Working Group attempts to address issues of human resources, research training and recruitment, clinical research, special needs for animal research, and high-cost technology, and recommends mechanisms for ongoing review, evaluation, and continued research planning.

For example, successful implementation and achievement of the goals of the Research Plan of the Diabetes Research Working group will require a cadre of exceptionally talented and dedicated researchers who bring the power of their intellects and expertise to bear on solving the puzzle of diabetes. In order to ensure that a national pool of high-quality biomedical researchers will be available in sufficient numbers to meet the needs of diabetes research, the Diabetes Research Working Group considers it essential to:

- Enhance development of established diabetes investigators, especially in high-risk and high-technology areas;

- Recruit and train scientists with recently completed postgraduate degrees (Ph.D./M.D.) in research areas related to diabetes, as well as in important related disciplines, and help them make a transition to mature investigators;

- Recruit and train individuals with interests in clinical research; and

- Increase the flow of potential trainees with interest in diabetes, beginning with pre-college and college/university programs, from all areas of science.